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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

HM11/0724

JACOBSON, D

ART UNIT	PAPER NUMBER
1652	30

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DATE MAILED: 07/24/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 4-6,8,20-21,23-25,27-29,31-41 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 4-6,8,20-21,23-25,~~8~~ 27-29,31-41 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☒ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-404-496/40517

Claims 4-6, 8, 20-21, 23-25, 27-29, and 31-41 are pending in the present application.

Applicants' response submitted June 22, 1998, has been considered. The arguments are not persuasive for the following reasons. Also, upon further consideration the following new grounds of rejection is deemed appropriate.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-6, 8, 20-21, 23-25, 27-29, 31-36, and 38-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses the complete amino acid and cDNA sequence of human tissue factor protein. The specification suggests deleting the transmembrane domain, residues 220-242, for example (page 13) or deletion the glycosylation sites (page 16). No other deletion variants are suggested by applicants. The examples do not describe construction of any deletion variants, only cloning and determining the sequence encoding human tissue factor protein.

Claims 4-6 and 8 are drawn to a tissue factor protein having at least amino acid residue one to at least amino acid 219. There is no basis in the specification for the phrase "at least"

residue one to "at least" residue 219. The metes and bounds of "at least" at not known. The specification does not specifically describe a variant consisting of only residues 1 to 219, nor does it specifically describe a molecule that ends at *any* point between residues 219-263. Therefore, the specification does not convey to one of skill in the art that applicants were in possession of the claimed tissue factor deletion variants.

Claims 20-21, 23, and 27-29 are drawn to a tissue factor protein that has the sequence from amino acid one to an amino acid between residues 219 and 263. As stated above the specification does not specifically describe a molecule that ends at any point between residues 219 and 263.

Claim 24 is drawn to a protein wherein the cysteine residues are substituted. The specification is silent as to specific substitutions and it is not certain applicants were in possession of proteins in which the cysteine residues had been substituted.

Claim 25 is drawn to a protein wherein the potential proteolysis sites are deleted. The specification does not describe specific proteolysis sites and the substitution or deletion of such sites. The specification does not convey that applicants were in possession of the claimed tissue factor variants.

Claims 31-36 and 38-41 are drawn to a tissue factor protein comprising amino acid one to amino acid 219. "Comprising" is open language and encompasses molecules that include additional residues. For example the claims include molecules that have an amino acid residue between residues 220 and 263.

Claim 37 is adequately described by the specification.

In their response of June 22, 1998, applicants traverse the previous new matter/written description rejection. Applicants assert the specification conveys that they contemplated deletion variants including deletion of the transmembrane domain and other amino acids. Applicants refer to Figure 5. Applicants assert that the specification conveys they were in possession of a tissue factor protein lacking the C-terminal region beyond amino acid 219. Applicants also refer to the Declaration by Dr. Konigsberg. These arguments and the declaration have been fully considered but are not deemed to be persuasive.

As discussed above, the specification describes specific tissue factor variants. The variant lacking residues 220 to 242 or 243 is adequately described by applicants. Other deletion variants are not described sufficiently so as to demonstrate that applicants were in actual possession of other variants at the time the application was filed. The specification does not convey clearly to one of skill in the art that applicants invented the specific proteins as claimed. Because the specification provides only a general method of producing tissue factor deletion and/or substitution variants, it does not provide a written description of *specific* tissue factor variants. Applicants do not provide a sufficient number of representative species to show they were in possession of the claimed invention.

Figure 5 depicts the hydropathy profile of tissue factor. The figure shows that a particular region, residues 220-243, is hydrophobic. This figure does not suggest deletion of any residues, hydrophobic or not. It only shows which region of the molecule is hydrophobic in nature.

The Declaration by Dr. Konigsberg has been considered. The declaration asserts that one of skill in the art would understand that the transmembrane domain would include residues from the C-terminal region. This argument actually confuses the issue. At the time the invention was made one of skill in the art would have assumed a transmembrane domain to be a hydrophobic region, usually situated between an extracellular and a cytoplasmic domain.

Spicer et al. (PNAS 84:5148-5152) describe the primary structure of human tissue factor. Spicer et al. teach that the protein sequence consists of three distinct domains: the extracellular (residues 1-219), the hydrophobic (residues 220-242), and the cytoplasmic (residues 243-263). See abstract. There is nothing to suggest that the hydrophobic or transmembrane domain includes residues from the C-terminal cytoplasmic domain.

Scarpati et al. (Biochemistry 26:5234-5238) describe the cDNA sequence encoding human tissue factor. Scarpati et al. also describe the primary sequence and structure of the protein. The predicted sequence consists of a signal peptide of 32 or 34 amino acids, a probable extracellular domain of 217 or 219 amino acids, a transmembrane domain of 23 amino acids, and a cytoplasmic tail of 21 amino acids. See abstract, page 5236. The reference provides no suggestion that the transmembrane domain includes residues from the C-terminal cytoplasmic domain.

Fisher et al. (Thrombosis Research 48:89-99) also describe cloning and expression of human tissue factor cDNA. The reference teaches that the protein contains a hydrophobic membrane spanning domain consisting of residues 220-243. The reference states, "We propose that this region, encompassing amino acids 220-243, comprises the membrane anchoring domain

of tissue factor." See paragraph bridging pages 94-95. Fisher et al. do not suggest in any way that the membrane spanning domain includes residues from the C-terminal region.

Therefore, based on the teachings of Spicer et al., Scarpati et al., and Fisher et al., there is no reason, based on the state of the art at the time the invention was made, to conclude that the "transmembrane domain" included anything other than residues 220-243. The Declaration by Dr. Konigsberg appears to contradict the teachings of the art. Based on the state of the art and the publications at the time the invention was filed, it is concluded that the transmembrane domain consists of residues 220 to 243 and no other residues. Claims to molecules lacking residues other than those of the transmembrane domain are not adequately described by the specification and the rejection stands.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Broze et al. (J. Biol. Chem. 250:10917-10920).

Broze et al. describe isolation of human tissue factor protein from brain tissue. The isolated protein had clotting activity. The reference does not disclose the amino acid sequence of human tissue factor protein. However, the primary structure is an inherent feature of the protein.

Claims 31 and 37 read on and include the complete native tissue factor protein. No difference is seen between the protein of claims 31 and 37 and the protein described by Broze et al. The claims are thus anticipated by the reference.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dian C. Jacobson whose telephone number is (703) 308-2973. The examiner can normally be reached Monday, Tuesday, and Thursday from 7:30 to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached at (703) 308-4216. The official FAX number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Dian Jacobson

DIAN C. JACOBSON
PRIMARY EXAMINER
GROUP 1600